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Measles Vaccines

Immunity to measles can be conferred by antibody. Thus measles is rare under 6 months of age if the mother is immune. Similarly, passive immunity is conferred by antibody in the form of normal gammaglobulin. The amount of antibody required to confer protection against the disease or modification of the infection is very low, barely detectable levels of neutralizing antibodies being found after the administration of protective doses of gammaglobulin. Circulating antibody is not, however, the only line of resistance to measles virus infection. Antibody is also required at the portal of entry and suggestive evidence of its importance will be considered later.

In addition, the importance of cell-mediated immunity is attested by the fact that children with antibody deficiency diseases, especially hypogammaglobulinæmia, usually respond perfectly normally to infection with measles virus. These children not only recover naturally from measles, but are subsequently immune to second attacks just like normal children. In contrast, children with leukæmia who have profound disorders of their immune responses including lack of cell-mediated immunity sometimes develop a chronic progressive, ultimately fatal form of measles virus infection known as Hecht's giant cell pneumonia.

The major fact is that natural measles is nearly always a clinically manifest infection and it confers a long-lasting and solid immunity against second attacks. The major reasons for this are that there is only one antigenic type of measles virus and that the incubation period is long so that during this period the anamnestic response mounted in a sensitized host eliminates the reinfecting virus before it causes disease.

The long duration of immunity, even in the absence of reinfection for sixty or more years, demonstrated by the observation in outbreaks in isolated communities that all those previously exposed to measles prove immune, has led to speculation that the virus may lie latent in the body and thus produce long-lasting immunity. The experience of isolated communities shows that any latent virus that exists is not epidemiologically important, because in these communities the disease dies out. Island studies show that a population greater than about 250 000 is required to sustain endemic measles. Therefore any virus which is latent cannot escape from the host again in an infectious form, such as occurs with herpes simplex or zoster-varicella viruses. None the less there is clear evidence that the virus can remain latent for many years in an immunologically privileged site like the brain only to reappear perhaps due to a failure of cell-mediated immunity. Such a reappearance is believed to be responsible for subacute sclerosing panencephalitis (SSPE).

The vaccines available against measles are nowadays, for practical purposes, living attenuated ones and of these there are now only two widely used, the Schwarz strain developed at Pitman Moore and the strain developed by Hilleman and his colleagues at Merck, Sharpe & Dohme. Both strains were derived from the Edmonston B strain. The original isolation and passage history is shown in Fig 1 (Dudgeon 1969). These strains were subsequently given a series of passages in chick embryo fibroblast cells at 32–33°C. The resultant vaccines are very similar in performance. In England another vaccine of basically the same sort was developed at the Wellcome Research Laboratories after 85 passages in chick embryo fibroblasts. All these vaccines are effective in producing antibodies against the disease. The only carefully controlled trial of effectiveness was done by the Medical Research Council using Schwarz vaccine either

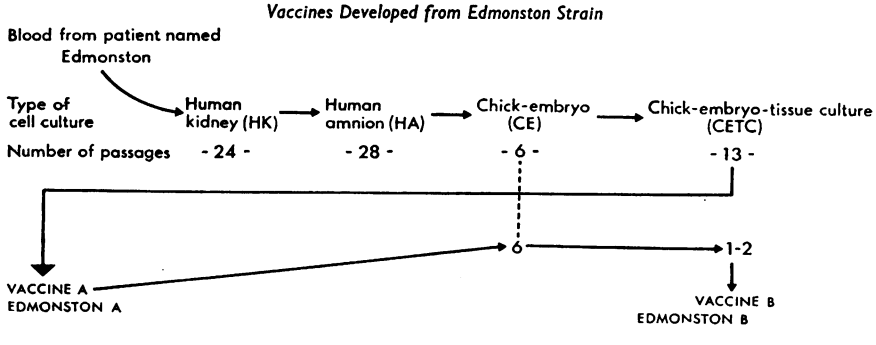

Fig 1 *Passage history of Edmonston vaccine strain and of vaccines derived from Edmonston A and B lines. (Adapted from Dudgeon 1969)*

Table 1

Adverse reactions to measles vaccine in the United Kingdom

	Measles vaccine adverse reactions				
Year	*Convulsions*	*Encephalitis*	*Measles-like illness*	*Other illnesses*	*No. of vaccinations (England & Wales)*
1968					120 833
1969	144 (82)●	31	—	—	1 740 636
1970					
1971	28 (52)	5	6	6	537 765
1972	17 (33)	2	4	10	513 210
1973	26	6	12	10	Not yet available
1974	10	3	9	4	Not yet available
Totals	225	47	31	30	

● Rate per million doses

alone or preceded by killed vaccine. It is interesting that the living vaccine gives slightly, though significantly, better protection than the killed followed by living schedule, although initially the results were similar. This could be due to lower titres of hæmolysin antibody using the killed living schedule.

In addition to the evidence from the formal trial it is clear that measles vaccine works in practice. At Willowbrook State School for mentally defective children, for example, the disease has been abolished for over a decade, whereas formerly it was a serious cause of illness and disability in this and similar institutions (Krugman 1971). The incidence of the disease has been greatly reduced wherever vaccine has been widely used. In the UK, for example, in 1972 there were 145 687 cases notified, compared with the 500 000 –750 000 cases reported annually before the vaccine was available. It is clear that if the vaccine is more widely used then the disease will disappear as have diphtheria and poliomyelitis as a result of effective immunization.

The picture so far presented is most satisfactory but is it the complete story? There are doubts on three aspects: reactogenicity, duration of immunity and long-term consequences. Each will be considered in turn.

Immediate Reactogenicity

Living measles vaccines produce a mild measles infection, characterized by fever, upper respiratory symptoms and rash. More rarely febrile convulsions or other central nervous symptoms may develop. The incidence of these complications was studied in the MRC trial for Schwarz vaccine and the results showed quite acceptable reactions. In large scale practice reactions have been relatively uncommon but two problems have caused concern:

(1) *Incidence of febrile convulsions:* The MRC trial showed clearly that the Schwarz vaccine produced many fewer reactions and febrile convulsions than the natural disease (1.9/1000 for living vaccine, 0.3 for controls and 7.7/1000 for cases of natural measles). The complications, however, showed a peak between 8 and 9 days after vaccination. Since 1968 adverse reactions have been reported to the Committee on Safety of Medicines (Table 1). The incidence of febrile convulsions is shown in Table 2. At first the reported incidence was about one per 12 000 vaccinations and later fell by about half perhaps due to a change of policy which delayed the use of vaccine until the second year of life. There is still a tendency to feel that these reactions to living vaccine are rather greater than is desirable but it seems unlikely that a better strain will be developed because of the cost and difficulty of introducing another strain. This is an aspect of vaccine development that we ought to ponder because innovation and improvement is definitely discouraged. Schwarz had a strain he thought might be marginally more attenuated but the effort to establish it seemed too formidable and development was abandoned.

(2) *Encephalitis:* One important aim of measles vaccine is to reduce the incidence of encephalitis. In the USA the data show clearly that there has been a steady decrease in measles encephalitis as the incidence of the disease declined (Krugman 1971). There is some cause for concern because in the USA, out of 59 cases of encephalitis of uncertain etiology, 45 were in the time interval 6–15 days after vaccination. There is, however, little proof of an etiological association. Continued and improved systems of surveillance are clearly required.

Table 2

Reported reactions to measles vaccine in the United Kingdom

	Convulsions	*Encephalitis*
Schwarz	57 (28)●	13
Beckenham 31	65 (68)	15

● Rate per million

Duration of Immunity

Krugman (1971) has produced data from Willowbrook where reinfection does not occur showing the decline in antibody levels with various vaccines; in general the fall-off is least following natural disease and greatest after use of the more attenuated vaccine strains. However, he has also shown that the anamnestic response occurs in children in whom antibody levels have fallen to undetectable levels before they are revaccinated. The MRC trial also shows continued and very satisfactory protection five years after vaccination. However, some doubts persist. First, there have been a number of outbreaks of measles in the USA and UK, so that after initial success there was some increase in the incidence of disease. Analysis of outbreaks shows that the protective effect of the vaccine is excellent, although a proportion of vaccinated children do get the disease, and outbreaks occur in highly immunized communities which suggests that reinfection and spread by vaccinated children may occur. In the follow up of the children in the MRC trial a total of 968 children have contracted the disease. This is 3% of those given living vaccine and 5% of those given killed-living schedule. Evidence for reinfection comes from studies of children in the community compared with those in Willowbrook. The children in the community do not experience the decline in antibody titres seen in those not exposed to reinfection. Similarly J Bell & J McQuillan (personal communication) have found that measles virus can be identified by immunofluorescence in nasopharyngeal secretions of some vaccinated children. These authors also found that virus could be identified in nasopharyngeal secretions up to a week after the appearance of a rash. Most of the vaccine failures can be ascribed to one or other of the following causes, but a few remain as true vaccine failures because in all studies antibody responses to vaccine have been less than 100%. The causes for failure that have been identified are:

(1) Vaccination under the age of 1 year when maternal antibodies interfere with the growth of vaccine virus.
(2) The simultaneous use of gammaglobulin where the response is often less satisfactory if the dose of gammaglobulin is too great.
(3) The use of killed vaccine before living vaccine has been found to be less efficient in giving protection in the MRC trial and serologically in Canadian trials.
(4) The vaccine is labile and observation in several clinics and pædiatricians' offices in the USA has revealed suboptimal handling of vaccine.
(5) The decline in antibody titres has been found to be greater with attenuated vaccines compared with natural disease, and the decline is greater with the more attenuated vaccines. However, it is usually maintained that two circumstances lessen the importance of these observations. First, it is found that the titres remain higher in children exposed to reinfection in the community than in those in institutions like the Willowbrook State School where the disease has been eliminated. Second, the long incubation enables an anamnestic response in a sensitized host to cope with reinfection.

Experiences with the related virus of distemper in dogs enjoins caution, because studies at Wellcome showed that distemper vaccine at the 250th passage level gives lower febrile reactions compared with the 125th level. Despite similar titres of neutralizing antibody the immunity provided was not as solid as shown by direct challenge in the laboratory. Similar experiences could result in man if more attenuated vaccines are developed. These experiences with canine distemper vaccine suggest that variations may occur in the quality of the antibody.

Norrby and his colleagues have found that antibody titres induced by killed vaccine are less effective than antibodies produced by natural infection. Thus titres of antibody produced by killed vaccine 50 times the effective level produced by passive protection may fail to confer immunity. This clearly implies that there is an antigen lacking in killed vaccine but present in the natural virus. Appleyard *et al.* (1971) identified an important protective antigen in extracellular vaccinia not present in intracellular virus which is the main material in killed pox virus vaccines. They also found that neutralization tests did not always detect this antigen. Something similar may be happening in measles. Norrby has adduced some evidence that the missing antigen is hæmolysin (Table 3): (1) The methods used to prepare killed vaccines destroy hæmolysin. (2) Antibodies to hæmolysin are not produced by killed vaccine in rabbits. (3) Children given killed vaccine in Sweden and Germany lack antibodies to hæmolysin. (4) Children given

Table 3

Hæmolysin inhibition titres after measles immunization (data from E Norrby)

Immunization	*Total HI > 20*	*No. with titre shown HLI < 10*	*HLI > 10*
KKK	15	11	4
Schwarz	18	1	17
KKK Schwarz	14	13	1
Natural measles	7	0	7

HLI titre determined after adsorption of HI with tween ether extracted HA. Sera collected between one month and 1½ years after vaccine

killed followed by living vaccine have no antibodies to hæmolysin. These observations argue strongly in favour of the importance of hæmolysin.

My colleagues Apostolov & Damjanovic (1973) have shown that the related Sendai virus can be killed by heating to 100°C for 20 minutes in the freeze dried state whilst preserving both the hæmagglutinin and hæmolysin, indeed the hæmolysin titre is increased. This technique could well be exploited to produce a killed measles vaccine which would be effective and free of the reactions associated with living vaccines both immediate and remote. The addition of the extra antigen may give durable protection and avoid the hypersensitivity reactions, sometimes severe, that were associated with early killed vaccine (Fulginiti *et al.* 1967). Whatever their exact mechanism, these reactions were due to the ability of living measles virus to multiply in a sensitized host. This could well be due to the absence of a protective antibody. Another explanation could be a lack of secretory IgA antibody in the respiratory tract so that large quantities of virus are produced locally in a sensitized host. Surveillance of the duration of protection afforded by measles vaccine must continue and if necessary booster immunization will have to be undertaken.

Long-term Consequences

The third concern about living measles vaccine is long-term consequences; for example, encephalitis, subacute sclerosing panencephalitis and multiple sclerosis. At present there is little hard information, but the incidence of CNS complications ascribable to measles seems to be declining in the USA. Moreover, experience at large pædiatric hospitals, like the Hospital for Sick Children in Toronto for example, shows that there has been a decline in the number of cases admitted for CNS complications of measles since the introduction of vaccine. It is too early as yet to decide about SSPE but so far as it goes the evidence collected in the UK does not support an increase in incidence as a result of using attenuated vaccine. Certainly the more attenuated virus, if it is like distemper virus in dogs, will multiply to a lower titre and spread less widely than the more virulent wild virus, and should therefore be less likely to produce this disease.

Evidence about the association of measles and multiple sclerosis does not at present warrant any change in vaccine policy. Measles is a serious disease of childhood and there is a possibility of reducing its incidence to insignificant levels as has been done previously by immunization for diphtheria, smallpox and poliomyelitis; there is also the likelihood that CNS complications of measles will be reduced. This will not happen, however, unless levels of immunization are increased. Thus in the USA a recent estimate puts the proportion of school age children vaccinated as 60%, and this compares with 88% vaccinated against poliomyelitis in the hey-day of the successful campaign against that disease. Similarly in this country less than 50% of children receive measles vaccine. If we wish to reduce measles infection then more children must be vaccinated; the choice is ours.

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DISCUSSION

Sir Charles Stuart-Harris pointed to the remarkable epidemiological changes in measles since 1968. The winter biennial epidemics had been converted into a summer endemicity. This itself might lead to a lesser complication rate. Nevertheless, as Dr J F Warin had experienced in Oxford, outbreaks could occur even in a highly vaccinated population. The measles vaccination programme had been hindered all along by the problem of vaccine reactogenicity and why this was a greater problem in Britain than in the USA was unknown. It remained to be seen whether there was any prospect of a less reactive vaccine or a return to a killed vaccine.

Professor P J Lachmann pointed out that a diminution in measles in children under 2 years old should lessen the future incidence of SSPE.

Dr Morley and **Dr Beale** both thought that measles was no more severe in adults than in children.

Professor H P Lambert (*London*), while agreeing with this view, pointed out that our experience of adult measles was small. If vaccine programmes were not extensive enough to eradicate measles, the average age at which the nonvaccinated acquired the disease would inevitably rise.

Dr Morley, replying to a question, said that the incidence of SSPE in Nigeria was unknown.

Dr E Norrby pointed out the good protection against measles afforded by gammaglobulin, even in minute amounts. Much more HI antibody induced by inactivated vaccine was needed for protection. Clearly some important protective component was lacking from killed vaccine. The exact nature of the immune response to combined killed-live vaccine was still obscure.